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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,980	10/28/2003	Thomas P. Jerussi	4821-528-999	3979

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EXAMINER	
SPIVACK, PHYLLIS G	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,980	JERUSSI, THOMAS P.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's Amendment filed November 29, 2006 is acknowledged. Claims 41-51 remain under consideration.

Rejections and objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are reiterations of those previously set forth. They constitute the only rejections being applied to the instant claims.

Response to Arguments

Applicant's arguments filed November 29, 2006 in response to the rejection of claims 41-51 under 35 U.S.C. 103 as being unpatentable over Young, J.W., WO 94/00047, or Young, J.W., WO 94/00114, and Luscombe et al., Neuropharmacology, have been fully considered but are not found persuasive.

Applicant presents the same argument as set forth in the Response filed May 25, 2006 that the three part test for *prima facie* obviousness has not been met with respect to motivation of the desirability to combine references, with a reasonable expectation of success, and wherein each limitation of the rejected claims is taught or suggested.

Applicants correctly assert that the Young documents are applied in the rejection of record under 35 U.S.C. 103 to show the optically pure (-) and (+) isomers of sibutramine. From this premise, Applicants argue one skilled in the art would not have acquired motivation from Luscombe to use didesmethylsibutramine for the treatment of depression. In Applicants' view no difference in pharmacological activity *in vivo* is observed for the metabolite.

Both Young documents ('114) and ('047) are drawn to the administration of optically pure stereoisomers and teach the importance of stereochemical purity in the

field of pharmaceuticals. The commercial product is a racemic mixture of sibutramine used in the treatment of depression. The optically pure (-) or (+) form of sibutramine exhibits a more rapid onset of action than the racemic form of the drug. Further, (-) or (+) sibutramine is useful for treating other pathologies as cerebral function disorders or in treating obesity. See page 10 in ('114). Administration of an optically pure form avoids adverse effects associated with the racemic mixture. The references provide ample motivation for one skilled in the art to appreciate the distinction and advantages between administration of the racemic mixture and an optically pure stereoisomer.

Luscombe teaches didesmethylsibutramine as an antidepressant to be more active, i.e., up to 100 fold more potent, than sibutramine as monoamine uptake inhibitors *in vitro*. Further, the pharmacological effects of sibutramine *in vivo* are mainly due to the activity of its primary and secondary amine metabolites. The primary amine metabolite is didesmethylsibutramine. Luscombe also teaches this metabolite results in fewer and less pronounced side effects than the tricyclic antidepressants.

In view of these collective teachings, one skilled in the psychological or psychiatric art would have been motivated to administer the active metabolite of sibutramine, didesmethylsibutramine, as the optically pure stereoisomer, with a reasonable expectation of treating depression.

In response to the rejection of record under 35 U.S.C. 102(b), Applicants argue Scott's teachings are not drawn to a patient having depression.

Scott presents a mammalian system wherein racemic didesmethylsibutramine is administered to a rat. See column 1, page 97, where Scott teaches the

pharmacological effects of sibutramine as an antidepressant are mainly due to the activity of the metabolite, didesmethylsibutramine.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 41-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young, J.W., WO 94/00047, or, Young, J.W., WO 94/00114, and Luscombe et al., Neuropharmacology.

Young teaches the administration of the optically pure (+) isomer of sibutramine in WO 94/00047 ('047) and the administration of the optically pure (-) isomer of sibutramine in WO 94/00114 ('114) to treat depression. See claim 1 in both documents. Further, Young teaches the importance of stereochemical purity in the field of pharmaceuticals where chirality is demonstrated. Some stereoisomers are safe and effective while others are teratogenic. In re Adamson et al., (CCPA 1960) 275 F2d 952, 125 USPQ 233.

Luscombe teaches metabolites of sibutramine (which is the tertiary amine), the secondary amine metabolite (BTS 54 354) and the primary amine metabolite (BTS 54 505), which is didesmethylsibutramine, to be considerably more active than sibutramine. See Figure 1, page 129, and Table 1 on page 131. A dosage range of 0.1-3.0 mg/kg is disclosed on page 130 under *Prevention of reserpine-induced ptosis in rats*. The references fail to teach optically pure enantiomers of didesmethylsibutramine.

However, in view of the combined teachings of Young and Luscombe, one skilled in the art of formulation chemistry would have been motivated to prepare and administer an optically pure enantiomer of didesmethylsibutramine with a reasonable expectation of success in treating depression. Such would have been obvious in the absence of evidence to the contrary because Young teaches antidepressant activity following the administration of either optically pure (-) sibutramine or optically pure (+) sibutramine. Luscombe teaches the close structural relationship of sibutramine and its metabolite didesmethylsibutramine, as well as the demonstration of antidepressant activity of the active metabolite of sibutramine, didesmethylsibutramine. Because didesmethylsibutramine is also optically active, one skilled in the art would have been motivated to resolve the R(+)- and S(-) enantiomers through no more than routine experimentation and compare their efficacy in treating depression to the racemic didesmethylsibutramine. It would have been reasonable to expect such R(+)- and S(-) enantiomers would exhibit a lower side effect profile or a faster onset of action.

As required by instant claims 43-45, the determination of both optimal dosage ranges and optimal modes of administration are parameters well within the purview of those skilled in the art through no more than routine experimentation.

With respect to claimed dosage ranges of the active agents in the instant methods, it is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(II). The determination of the optimum dosage regimen to employ with the presently claimed

active agents would have been a matter well within the purview of one of ordinary skill in the art. Such determination would have been made in accordance with a variety of factors. These would have included such factors as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered a part of a drug combination. Thus, in the absence of evidence to the contrary, the currently claimed specific dosage amounts and dosage regimens are not seen to be inconsistent with the dosages that would have been determined by the skilled artisan.

The additional administration of drugs, as required by claims 48 and 49, such as selective serotonin reuptake inhibitors, serotonin modulators, hypnotics, sedatives, CNS stimulants, are well established in the prior art for the treatment of depression.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by Scott et al., British Journal of Pharmacology.

Scott teaches a method of treating depression comprising administering didesmethylsibutramine (BTS 54 505), a metabolite of sibutramine. Didesmethylsibutramine has a similar pharmacological profile to the parent compound

in vivo; however, the metabolite is very much more potent than the parent compound. Instant claim 41 is drawn to the administration of a racemic mixture of didesmethylsibutramine in a mammalian system.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this Final Action is set to expire THREE MONTHS from the mailing date of this Action. In the event a first reply is filed within TWO MONTHS of the mailing date of this Final Action and the Advisory Action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the Advisory Action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the Advisory Action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this Final Action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached from 10:30 to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis Spivack

April 14, 2007

Phyllis Spivack
PHYLLIS SPIVACK
PRIMARY EXAMINER